REMARKS

This Reply is submitted in response to the final Office Action dated June 19, 2001. Entry of the amendments and remarks made herein is respectfully requested pursuant to 37 CFR §1.116(b), in that the amendments and evidence submitted simplify the issues for appeal. While Applicants are hopeful that the evidence and arguments presented will cause the Examiner to re-evaluate her position, if the Examiner is not willing to negotiate acceptable claim language or allow the present claims on the basis of this evidence, Applicants respectfully request that she at least enter the material into the file so that the Board may have access to all the relevant information on appeal.

New claims 39-42 were added above in order to define the claimed DNA according to the structural characteristics disclosed in the specification. Support for these claims may be found at page 9, first full paragraph. No new matter has been added. Claim 35 was amended to clarify that this claim is directed to isolated DNAs comprising open reading frames defined in the specification, specifically, those of Figure 2, 11A and 11B.

Claims 3, 11-15, 22, and 24-28 stand rejected under 35 U.S.C. §101 as allegedly lacking a specific, substantial and credible utility or a well-established utility. A corresponding rejection has been made under the enablement provision of first paragraph of §112, because one skilled in the art would allegedly not know how to use the claimed invention due to the alleged lack of utility. Applicants respectfully traverse these rejections.

Applicants maintain their arguments of record with regard to the utilities disputed thus far. However, applicants traverse in particular on the following grounds. The Examiner has dismissed the noted homology of the encoded proteins to the TGF-ß superfamily as failing to provide the requisite utility, apparently because the biological activities of this family are "diverse." The Examiner further alleges that it could not have been predicted which activity the GDF-1 protein would have, if any (see the Office Action, 6-19-01 at page 4). Therefore, the DNAs encoding GDF-1 and claimed methods of producing the protein also allegedly lack utility.

According to the comments and answers recently published in the Federal Register with the new utility examination guidelines (FR, Vol. 66, No. 4, January 5, 2001), it is perfectly acceptable to assert a specific, substantial and credible utility on the basis of "homology to existing nucleic acids or proteins having an accepted utility." Furthermore, according to this Notice, a rigorous correlation is not necessary; only a "reasonable"

correlation (see the FR Notice, page 1096, middle column continuing into right-hand column). As stated therein, "When a class of proteins is defined such that the members share a specific, substantial, and credible utility, the reasonable assignment of a new protein to the class of sufficiently conserved proteins would impute the same specific, substantial, and credible utility to the assigned protein" (with emphasis). Id.

According to the new utility guidelines, "the asserted utility must be accepted by the examiner unless the Office has sufficient or sound reasoning to rebut such an assertion" (with emphasis) Id. The Examiner rejects the asserted utility on the basis that the members of the TGF-ß family exhibit diverse activities. However, the Examiner provides no evidence that those of skill in the art at the time the invention was made would have believed that members of the superfamily exhibit such diverse activities as to preclude prediction of function. In fact, according to an abstract by Akhurst published in 1990 (just prior to the effective filing date of the application) and attached hereto, there had been five type beta transforming growth factors (TGF betas) identified at that time, each of which was found to play "a pivotal role in embryonic processes." Furthermore, according to Akhurst et al., there was sufficient evidence to assign TGF beta 1, beta 2 and beta 3 a role in mammalian developmental processes, including control of growth, differentiation, tissue induction and morphogenesis.

Thus, at the time the invention was made in 1990, one of skill in the art would have reasonably predicted that a member assigned to the TGF-ß superfamily would play a role in embryonic development, and in the growth and differentiation of tissues, given that the five members identified at that time were shown to play a pivotal role in embryonic development. Indeed, according to the instant specification at page 1, "a growing number of polypeptide factors playing critical roles in regulating differentiation processes during embryogenesis [had] been found to be structurally homologous to transforming growth factor ß." On that basis, and in view of the homology of GDF-1 to TGF-ß, the present inventor predicted that the GDF-1 protein was likely to play an important role in mediating developmental decisions related to cell differentiation (see page 2, lines 25-29). Moreover, it was perfectly reasonable on the basis of that prediction and the homology demonstrated to assert that the claimed protein would find utility in prenatal screens to detect developmental abnormalities, as disclosed on pages 12-13 of the specification.

The Examiner has provided no evidence to suggest that these predictions, which were based on the known activities of TGF-ß at the time, were unreasonable. She has presented no

evidence to suggest that TGF-ß activities were thought to be so diverse at that time so as to make these predictions unreasonable. Furthermore, the argument that one could not have predicted the role of the GDF-1 protein based on homology with this superfamily should be re-evaluated in view of recent evidence with GDF1-/- knock-out mice that demonstrates that, in fact, Applicant's predictions were correct.

For instance, as the present inventor and others have shown in a recently published paper (Rankin et al., 2000, Regulation of left-right growth patterning in mice of growth/differentiation factor-1, Nature Genetics 24: 262-66), GDF-1 plays a pivotal role in embryogenesis. A knockout mouse was generated in order to examine the biological function of GDF-1, which exhibited a spectrum of defects related to left-right axis formation in embryos, including misplacement of internal organs (Fig. 2), developmental defects in organs and cardiac abnormalities (Fig. 3). The authors concluded that these findings indicate that GDF-1 is essential for proper establishment of the left-right axis in mice, and is required for the expression of many genes expressed downstream from gdf1 during development.

Thus, results with the GDF1-/- knockout mouse prove that GDF-1 is required for the proper development and positioning of organs during embryogenesis. This is consistent with the function of GDF-1 predicted in the specification (page 2, lines 25-29), and the results in the specification showing the expression of GDF-1 during embryogenesis (see Example 4 and Fig. 6). These results also suggest that the asserted utility of GDF1 in prenatal screens for abnormal development is a reasonable utility for the disclosed protein, given that aberrant expression of GDF-1 has now been shown to have significant and substantial effects on embryonic development. A reasonable utility for the GDF-1 protein translates to a reasonable utility for the DNA encoding that protein, as well as for vectors, host cells and methods of recombinant production.

Applicants' assignment of GDF-1 to the TGF-ß superfamily has been substantiated by the numerous GDF proteins that have been subsequently identified and likewise assigned to this superfamily. Thus, others of skill in this art have followed Applicant's lead, and have corroborated that classification (see the attached PubMed printout of scientific abstracts published after the present invention was filed). In contrast, the Examiner has presented no evidence that GDF-1 should not be classified in the TGF-ß family. Furthermore, it is pertinent to point out that numerous other GDF proteins have been patented on the basis of their homology with the TGF-ß superfamily. See, e.g., USP 5,808,007 (GDF-3); USP

5,801,014 (GDF-5); USP 5,770,444 (GDF-6); USP 5,986,058 (GDF-7); USP 5,827,733 (GDF-8); USP 5,821,056 (GDF-9); USP 5,831,054 (GDF-12); USP 6,120,760 ("Growth and Differentiation Factors of the TGF-ß Superfamily"). Thus, Applicants respectfully stress again that it appears they are being held to a different standard than others have been held to before.

Thus, it is clear from the issued patents noted above that members of the TGF-ß superfamily, including GDF proteins, have a well-established utility. Furthermore, at the time the application was filed, the TGF-ß superfamily was known to comprise proteins involved in embryonic development, a function that Applicants predicted that GDF-1 would share. Further, Applicants have now shown that GDF-1 does possess the predicted function, thereby supporting the disclosed utilities, i.e., use in prenatal screening for developmental defects. And as noted above, according to the new utility examination guidelines, it is perfectly acceptable to predict a specific, substantial and credible utility on the basis of homology to existing nucleic acids or proteins having an accepted utility.

As acknowledged in the Office Action, GDF-1 proteins are 26-52% similar to TGF-ß family members on the amino acid level. Moreover, according to the specification at the paragraph bridging pages 19-20, GDF-1 contains all of the invariant amino acids present in the C-terminal 122 amino acids of other TGF-ß superfamily members, including the seven characteristic cysteine residues as well as many of the other most highly conserved amino acids. For instance, like the other family members, the C-terminal portion of the predicted GDF-1 polypeptide is preceded by a pair of arginine residues at positions 236-37. Thus, GDF-1 contains sufficient homology to be assigned to the TGF-ß superfamily, as substantiated by the similar assignment of other GDF proteins.

Thus, given that the new utility examination guidelines explicitly state that it is permissible to assert a credible utility on the basis of homology to a family of proteins having a well-established utility, and given that the inventors predicted and have now proven that GDF-1 would share the utility that had been well-established for members of the TGF-ß superfamily at the time the application was filed, Applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. §101 and the enablement provision of §112, first paragraph.

Claims 3, 11-15, 22 and 24-38 were also rejected under the written description section of 35 U.S.C. §112, first paragraph. According to the Office Action (page 5), claims 24, 25

and 35 include sequences outside the open reading frame which have not been disclosed and are therefore not described. These claims are directed to isolated DNA segments comprising specific sequences explicitly disclosed in the specification. If the Examiner's standard was to prevail, every inventor discovering a novel DNA sequence would be limited to only that novel gene sequence, and would not be able to protect the use of that sequence once it was cloned into any vector or other larger piece of DNA. This seems unusually strict, and Applicants respectfully request that the Examiner support her position with established case law or other examination guidance material. In this regard, claim 35 has been amended above such that this claim reads only on isolated cDNA sequences.

The Office Action also criticizes claim 31, which defines the claimed DNAs according to hybridization conditions, in that, Example 5 of the specification shows that even at high stringency conditions, additional bands were detected in addition to the predominant band. Applicants respectfully submit that additional faint bands will frequently be detected in any hybridization experiment, but the fact that a specific prominent band can be detected shows the specificity of the hybridization.

Further, Applicants respectfully note that the stringency conditions noted in claim 31 (0.1 X SSC wash) are actually considered to be high stringency conditions. For instance, as discussed in the legend to Figure 14 on page 9 of the specification, human genomic DNA probed with human GDF-1 coding sequences was washed in 0.2 X SSC, whereas human genomic DNA hybridized with murine GDF-1 coding sequences was washed in 2X SSC. Thus, the conditions recited in claim 31 are suitable for identifying substantially identical sequences (as disclosed on page 10 of the specification), but a 2X SSC wash may be used to analyze cross-species hybridization. These alternative hybridization conditions are recited in new claim 39 as a means to define the claimed DNAs, and such a scope is clearly warranted in view of the experiments depicted in Figure 14.

The Office Action also alleges that no structural features were identified that could be used to define a GDF-1 protein, and the application teaches no assays for functional identification. Applicants note that the specification discloses that the human and murine GDF-1 proteins are 87% identical in the region beginning with the first conserved cysteine and extending to the C-terminus (see page 31, lines 19-20). Thus, this specific domain of GDF-1 is quite highly conserved across species, and would constitute a structural feature for identifying a GDF-1 protein.

Furthermore, the instant specification does disclose an assay for identifying a GDF-1 gene, in that a probe generated from the full length murine open reading frame of GDF-1 hybridized specifically to the human gene in Southern hybridization (see Fig. 14 legend at page 9, and the relevant discussion at pages 31-32). As also shown in Figure 5, even at high stringency, a murine GDF-1 probe identified a single prominent band in both human and hamster genomic DNA. The genomic sequences identified by these hybridization experiments could be readily cloned and sequenced using techniques that were well known at the time the application was filed. In this regard, Applicants note that new claim 39 has been submitted above, which defines the claimed DNA according to the hybridization assay disclosed in the specification.

The Office Action inquires as to why the structure of genomic sequences should be considered to be described in the specification. In the past, the Examiner has cited a variety of case law for the premise that the actual DNA sequence itself must be disclosed for every sequence falling within the scope of the claims, including *University of California v. Eli Lilly*, 43 USPQ2d1398. Applicants respectfully submit that the merits of each case must be examined on a case-by-case basis, and *Lilly* does not suggest otherwise. Moreover, *Lilly* is only relevant to the particular circumstances surrounding that case, which happened to occur at a time when the art of biotechnology was much less developed than it is now. In fact, the present application was filed after the publication of the popular Sambrook Molecular Cloning manual (2nd edition), which standardized many of the cloning procedures now used to identify and isolate genomic DNAs. Indeed, given the existence of the Sambrook manual at the time the present invention was filed, those of skill in the art would have surely seen that the inventor was in possession of the genomic DNA for the GDF-1 protein upon reading the present disclosure.

For instance, in the Federal Register publication of the Written Description Guidelines for Examination (FR, Vol. 66, No. 4, page 1099, January 5, 2001), the Office answered one comment by stating that "Actual reduction to practice may be crucial in the relatively rare instances where the level of knowledge and level of skill are such that those of skill in the art cannot describe a composition structurally, or specify a process of making a composition by naming components and combining steps" (with emphasis, see page 1101). In fact, the actual Guidelines state at page 1106 that:

> An applicant may show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail. If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met.

Footnote 42 of the Guidelines further defines some identifying characteristics for biomolecules to include sequence, structure, binding affinity, binding specificity, molecular weight, length, unique cleavage by particular enzymes, detailed restriction maps, a comparison of enzymatic activities, or antibody cross-reactivity (see page 1110 of the FR Notice). If binding specificity is one acceptable characteristic to be combined with sequence data for satisfaction of the written description requirement, then hybridization experiments showing specific hybridization with a disclosed sequence should also be sufficient.

That hybridization to a genomic sequence should be sufficient to satisfy the written description requirement is further evidenced by the fact that it was common practice at the time to isolate the genomic DNA following similar hybridizations to a genomic library. The Guidelines specify that such common techniques need not be described, because one of skill in the art would be familiar with such techniques and would incorporate such knowledge into his understanding as to what the inventor possessed at the time of filing. For instance, according to the attached pages from Sambrook et al., 1989, Molecular Cloning: A Laboratory Manual (2nd edition), libraries generated from mammalian genomic DNA had been in use since the mid-1970's for cloning mammalian genes (see page 9.2). And according to the teachings on page 9.3, it was well-known at the time this Manual was published that one could use libraries of randomly cleaved DNA to "walk" along the eukaryotic chromosome starting with a single specific probe, in order to isolate segments of

DNA in and around target sequences without knowledge of the location of surrounding restriction sites.

Thus, having full knowledge of the techniques that were well-known in the art at the time the invention was made, one of skill in the art reading the present disclosure and seeing that the disclosed coding sequences could be used as a probe to specifically identify genomic sequences by hybridization would have immediately seen that the present inventor was in possession of both coding sequence and genomic DNA comprising coding sequence. Furthermore, given the extent of homology between human and mouse GDF-1 shown in the specification, and the fact that probes generated from these sequences cross-hybridize specifically to the GDF-1 gene in alternative species using hybridization conditions specifically defined in the disclosure, it would be clear to those skilled in the art upon reading the present disclosure that Applicants were in possession of the claimed invention at the time the application was filed. In view of these remarks, reconsideration and withdrawal of the rejection under 35 U.S.C. §112, first paragraph, written description, is respectfully requested.

All issues raised by the Office Action dated June 19, 2001, have been addressed in this Reply. Accordingly, a Notice of Allowance is next in order. If the Examiner has any further questions or issues to raise regarding the subject application, it is respectfully requested that she contact the undersigned so that such issues may be addressed expeditiously.

Respectfully submitted,

Pillsbury Winthrop LLP

By: _____
Bonnie Weiss
Registration No. 43,255

1600 Tysons Boulevard
McLean, Virginia 22102
(703) 905-2000 Telephone
(703) 905-2500 Facsimile

Date: October 19, 2001

Attorney Reference: 020055-0241800

APPENDIX: VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims

35. (Amended) An isolated DNA segment encoding mammalian GDF-1 protein which comprises [a nucleotide sequence as defined in an] the open reading frame for GDF-1 as shown in Figure 2 or Figure 11A or Figure 11B.